REMARKS

Applicants respectfully request reconsideration in view of the foregoing amendments and the following remarks.

I. STATUS OF THE CLAIMS

Claim 1 is amended to recite specific embodiments. In particular, the claims now recite that the organic complex and antigen are "associated only by electrostatic interaction," as taught at page 10, lines 1-2. Claims 53-55 are amended to depend from claim 1. Claims 56-61 are added to recite specific embodiments described, for example, at page 14, last paragraph (for claim 56), at page 13, third paragraph (for claims 57 and 58), at page 1, third paragraph (for claims 59 and 60), and at page 12, second paragraph (for claim 61). (All page number references are to the pages of the substitute specification.)

With regard to claim 61, Applicants note that MPEP § 2173.05 provides that when "alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." Here, because the specification teaches (for example, at page 12) that the organic carrier may be an adjuvant such as, among other adjuvants, liposomes, the specification supports embodiments where the organic carrier does not comprise a liposome, as recited in claim 61.

These amendments are made without prejudice or disclaimer and Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications with the same rights of priority as the instant application.

Upon entry of the amendments, claims 1, 3, 12-17, and 53-61 will be pending. These claims are presented for reconsideration.

II. OFFICE INTERVIEW

Applicants thank Examiner Le for the courtesies extended during the Office Interview on May 12, 2009. Applicants' statement of the substance of the interview is provided here, in accordance with MPEP § 713.04. As reflected in the Interview Summary pending and proposed claims were discussed as were the cited references. In particular, as discussed in

more detail below, Applicants explained the cited references' failure to teach or suggest an electrostatically-associated immunogenic complex as claimed, where the organic complex and antigen are associated only by electrostatic interaction.

III. OBVIOUSNESS REJECTION #1

Claims 53 and 54 stand rejected under 35 U.S.C. § 103(a) over WO 96/33739 ("Garcon"). Applicants respectfully traverse this rejection inasmuch as it may be applied to the instant claims.

As reflected in independent claim 1, the pending claims are directed to an electrostatically-associated immunogenic complex comprising:
(A) a negatively-charged organic complex that comprises a saponin and a sterol, and
(B) a positively-charged antigen, where
the organic complex and antigen are associated only by electrostatic interaction.

As discussed during the Interview, and as taught in the specification, "[t]here is an increasing belief that co-delivery of antigen and adjuvant to the same antigen-presenting cell (APC) is preferable . . . for induction of appropriate immune responses." Specification, page 1. The electrostatically-associated immunogenic complexes of the present invention satisfy this need in a way that is novel and non-obvious over the cited references. For example, there is no teaching or suggestion of an immunogenic complex where a negatively charged organic complex and positively charged antigen are associated only by electrostatic interaction. Moreover, as discussed during the interview, the ability of an immunogenic complex based solely on electrostatic interaction to withstand *in vivo* conditions and induce a cytotoxic T-lymphocyte response (as illustrated in the examples) was surprising and unexpected.

Garcon does not teach or suggest an electrostatically-associated immunogenic complex as recited in the claims. As discussed during the Interview, Garcon is directed to the discovery that formulating a saponin, such as QS21, with a sterol, such as a liposome containing cholesterol, overcomes some of the disadvantages of saponins, such as their lytic effect, and has a stabilizing effect. *See, e.g.*, Garcon, pages 1, 6 and 8. Garcon describes a

general approach that does not distinguish between positively charged and negatively charged antigens, but instead is taught to be useful for any "antigen or antigenic composition capable of eliciting an immune response against a human or animal pathogen." Garcon, page 3. Because Garcon does not distinguish between positively charged and negatively charged antigens, it simply cannot suggest the claimed electrostatically associated immunogenic complexes, because such complexes would not be possible with negatively charged antigens.

Garcon indicates that when QS21 is bound to liposomes, it may impart a negative charge. However, Garcon does not teach or suggest that such a negatively charged construct is complexed with a positively charged antigen by electrostatic interaction only. To the contrary, Garcon teaches that its antigens "can be contained within the vesicle membrane or contained outside the vesicle membrane." Garcon, page 2.

The Office Action states that the HSV glycoprotein D antigen disclosed in Garcon is "a positively charged protein." Applicants do not understand the basis for this assertion. It is Applicants' understanding that full-length HSV glycoprotein D (without the signal sequence) has an overall negative charge of -3, while the truncated form of HSV glycoprotein D has an overall negative charge of -6. In any event, Garcon does not teach an immunogenic complex wherein an HSV glycoprotein D antigen is associated with a negatively charged organic complex by means of electrostatic association only.

Garcon also mentions the use of ISCOM structures, but provides no express teachings on how ISCOMs would be used in its compositions. Pages 4-5 of Garcon cite references that describe methodoliges that can be used in making its vaccines. Page 5 cites U.S. Patent 4,372,945 and U.S. Patent 4,474,757 for "[c]onjugation of proteins to macromolecules." Notably, the '945 and '757 patents disclose covalent conjugation methodoligies. (Copies of these patents are attached hereto for the Examiner's convenience). Thus, these teachings could not suggest the present invention, which relies on an electrostatic association between a positively charged antigen and negatively charged organic complex.

Moreover, the Examiner should understand that, at the time of the present invention, the art taught several different ways to attach antigens to ISCOMs, including by hydrophobic

interaction and covalent attachment. For example, Sjolander & Cox, *Adv. Drug. Deliv. Rev.* 34: 321-38 (1998) (copy attached) describes a hydrophobic interaction-based dialysis method that involves the incubation of components with detergent followed by removal of detergent to formation ISCOM. *See, e.g.,* Sjolander at pg. 326. For the described method to be effective, mixed micelles comprising saponin, cholesterol, phospholipid and protein are induced by addition of detergent. Removal of detergent by, *e.g.*, dialysis results in the formation of ISCOMs, provided that the protein has hydrophobic regions to participate in the formation of the mixed micelles, which are the required starting point for ISCOM formation. Figure 1 of Sjolander shows spikes of haemaglutinin incorporated into ISCOMs via their hydrophobic regions in accordance with this process.

Barr et al., *Adv. Drug. Deliv. Rev.* 32: 247-71 (1998) (copy attached), focuses on hydrophobic interactions and mentions covalent chemical coupling as an alternative for non-amphipathic molecules. *See, e.g.,* Barr at pg. 254. Other references submitted herewith further support Applicants' position:

Cox & Coulter, *BioDrugs* 12: 439-53 (1999) (copy attached), provides a table (Table I) of "[m]echanisms whereby immunogen and adjuvant can associate." ISCOMs are listed as examples of hydrophobic interactions, covalent bonding and chelation ("iscomatrix"), and are ***not*** listed as an example of electrostatic interaction. *See, e.g.,*Cox & Coulter (1999) at pg. 441.

Cox & Coulter, *Vaccine* 15: 248-56 (1997) (copy attached), describe immunogenic ISCOMs as "ISCOMs into which protein or other immunogenic molecules have been incorporated," and teach that "[i]t is important to incorporate immunogen into ISCOM for an effective CTL response." In contrast, they describe aluminum salt gels as being "bound by electrostatic interaction" to immunogens. *See, e.g.,*Cox & Coulter (1997) at pg. 250-51.

Cox & Coulter, "Advances in Adjuvant Technology and Application," in ANIMAL PARASITE CONTROL UTILIZING BIOTECHNOLOGY (Yong, ed.) (CRC Press, 1992) (copy attached), teaches that peptides can be incorporated into ISCOMS "either directly or by chemical coupling to a carrier protein . . . after incorporation of [the] protein," and teaches

modifications of peptides to enhance hydrophobic interactions to facilitate incorporation into ISCOMS. *See, e.g.,* Cox & Coulter (1997) at pg. 60.

None of these references, and none of the references cited in the Office Action, teaches an immunogenic complex where the organic complex and antigen are associated by electrostatic interaction only, as recited in the instant claims.

Claims 53-58 are separately patentable over Garcon. These claims recite embodiments where the negative or positive charge of the organic complex or antigen, respectively, has been modified to be increased. Garcon does not teach or suggest such modifications. While the Office Action cites page 2 of Garcon in this regard, the cited passage mentions only the use of a "charged lipid" to increase the stability of the liposome. It does not provide any guidance on whether the lipid should be positively or negatively charged. Moreover, when Garcon suggests that QS21 may impose a negative charge on the liposomes, it does not teach or suggest further increasing the negative charge of the QS21-liposome complex. *See, e.g.*, Garcon, page 11. Thus, Garcon does not teach or suggest increasing the negative charge of a negatively charged organic complex that comprises a saponin and sterol, as recited in claims 54 and 57, certainly does not teach or suggest increasing the positive charge of a positively charged antigen as recited in claims 53 and 55, and in no way teaches or suggests the specific modifications recited in claims 56 and 58.

In view of the foregoing, Applicants respectfully urge reconsideration and withdrawal of the §103 rejection based on Garcon.

IV. OBVIOUSNESS REJECTION #2

Claims 1, 3, 12-17 and 55 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Garcon in view of WO 98/36772 ("MacFarlan"). Applicants respectfully traverse this rejection inasmuch as it may be applied to the instant claims.

The inability of Garcon to teach or suggest the claimed invention is shown above. MacFarlan does not remedy the deficiencies of Garcon. As discussed during the Interview, MacFarlan uses chelation to form an immunogenic complex that comprises, for example,

ISCOMATRIX and an antigen. Thus, MacFarlan is not particularly relevant to the pending claims.

The Office Action cites MacFarlan's use of hexa-histidine tags as a modification that would increase the positive charge of a positively charged antigen. Applicants respectfully disagree. Histidine has a pKa of 6.0, and so is positively charged at a pH of 6.0, but is neutral or uncharged at a physiological pH.

In view of the foregoing, Applicants respectfully urge reconsideration and withdrawal of the §103 rejection based on Garcon and MacFarlan.

V. DOUBLE PATENTING

Claims 53 and 54 stand provisionally rejected on grounds of obviousness-type double patenting over claims of copending U.S. application serial No. 10/622,470. Applicants respectfully defer this rejection until claims in at least one of the applications have been found to be otherwise allowable.

VI. CONCLUSION

Applicants believe that this application is in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned attorney by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for

such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 8, 2009

By

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288